REMARKS

Status of the Claims

The Office Action of December 3, 2008 presents the examination of claims 1, 2, 6, 8, 15-17, 19 and 21-35. Claims 1-2, 6, 8, 15-17, 19, 21-25, 28-29, 31, and 36 have been canceled; claims 26, 27, 30, 32-35 are currently amended; and new claims 37-45 are added.

Amended claim 26 now defines the concentration of the components cited in each original step and additional conditions such as temperature and stirring, etc. Support for the amendments to claim 26 is explained below:

- support for the phrase "*10% to 50% w/w*" in amended claim 26 (a) is found at original claim 4 of the application as filed;
- support for the phrase "*between 30°C and 45°C*" in amended claim 26 (a) is found at page 22, line 18 of the application as filed;
- support for the phrase "*not higher than 40°C*" in amended claim 26 (c) is found at page 18, line 2 of the application as filed;
- support for the phrase "*in an amount ranging from 5.0 to 20% w/w*" in amended claim 26 (d) is found at page 12, line 10 of the application as filed;
- support for the phrase "*in an amount ranging from 20 to 40% w/w*" in amended claim 26 (d) is found at page 12, line 29 taken together with the example 19 of the application as filed;
- support for the phrase "*in an amount ranging from 0.001 to 2.0% w/w*" in amended claim 26 (d) is found at page 13, lines 19-20 of the application as filed;
- support for the phrase "*in an amount up to 60% w/w*" in amended claim 26 (d) is found at page 14, line 2;
- support for the phrase "*in an amount up to 0.5% w/w*" in amended claim 26 (d) is found at page 14, lines 11-12 of the application as filed;

- support for the phrase "until the remaining quantity of alcoholic solvent is between 5% and 20% w/w of the composition" in amended claim 26 (e) is found at page 12, line 7 of the application as filed;
- support for the phrase "*in an amount ranging from 0.1 to 20% w/w*" in amended claim 26 (f) is found at page 13, line 11 of the application as filed;
- support for the amended claim 26 (g) is found at page 18, lines 19-20 of the application as filed.

Claim 35 is amended to more clearly recite the alternatives presented.

The features disclosed in claims 28 and 29 have been added to the amended claim 26.

New claims 37 to 45 define the composition obtained by the process claimed. Support for new claims 37, 38, 39, 40, 41, 42, 43, 44, and 45 is found, for instance, in previously presented claims 1, 2, 6, 8, 15, 16, 17, 19, and 21, respectively.

No new matter has been added.

Status of the Application

After Applicants' September 14th, 2007 Amendment, the Examiner has maintained the following rejections:

a. The obviousness rejection over Lipari et al (US Patent 6,232,333) in view of Bailey et al (US Patent 6,008,228);

b. The obviousness rejection over Lipari in view of Bailey as above, and further in view of CUBoulder Organic Chemistry Undergraduate Courses, Lab Techniques;

c. The indefiniteness rejection of claims 26-36, of the claimed methods of manufacturing the compositions that do not state a specific concentration, weight, or final product form as an endpoint.

(Office Action, page 2)

1. Objection to the Specification

The Examiner objected to the specification as failing to provide antecedent basis for claim 25. Applicants have canceled claim 25; thus this objection is moot.

2. Claim rejections under 35 USC §103

2 (a). Lipari et al (US Patent 6,232,333) in view of Bailey et al (US Patent 6,008,228)

The Examiner maintained the rejection of claims 1-21 and also imposed new rejections of claims 22-25 under 35 USC § 103(a) as being unpatentable over Lipari in view of Bailey. Applicants' arguments of the prior response were considered not persuasive; the Examiner asserts that they were directed to individual aspects of the prior art documents but not to their teachings in combination. (Office Action, pages 4 and 9). Applicants respectfully traverse.

The Examiner stated that "*a reference is good not only for what it teaches by direct anticipation but also for what one ordinary skill in the art might reasonably infer from the teaching.*" (Office Action, page 6). So, the Examiner has the opinion that one ordinary skilled in the art would be motivated to try the present application composition with reasonable expectation of success in view of the Bailey's teachings.

However, the Examiner must recognize the fact that the teachings of Bailey are not sufficient to provide a suitable composition of ritonavir at the concentration recited in the instant claims. Applicants have pointed this out in the present application (see below):

> *The application WO 96/39142 describes a liquid composition for the administration of several protease inhibitors, among them ritonavir, employing a mixture of mono and diglycerides of C_8-C_{10} saturated fatty acids as organic solvent. Despite the inclusion of ritonavir in this document, the examples described compositions only for saquinavir. Experimentally, this composition is inadequate to supply stable composition of ritonavir, mainly if we consider compositions having high concentrations, for example 200mg/1g of the composition. Another negative aspect for this*

*composition is the high temperature needed for the complete dissolution of ritonavir in the described excipients which may lead to a thermal degradation of this drug. (*page 8, lines 6-18 of the specification as filed*).*

The Examiner has plainly simply used hindsight reconstruction of the invention, using the claims as a template, to select the various ingredients of the presently claimed composition from the prior art. This is plainly evident from the comparison of the instant invention against the prior art references provided in Applicants' prior Amendment (pp 15-16). Such an approach to asserting *prima facie* obviousness of a claim has been repeatedly rebuked by the Court of Appeals for the Federal Circuit and should not be engaged in presently.

Considering the Bailey reference, a person of ordinary skill in the art at the time the claimed invention was made might reasonably infer that a pharmaceutical composition of proteinase inhibitors would require a high amount (40-80% w/w) of a mixture of mono and diglycerides of medium chain (C_8-C_{10}) which must contains at least 70% of monoglycerides (claim 1) or about 83 to 95% of monoglycerides (claim 7). In addition, the document teaches that the weight ratio of monoglyceride to the proteinase inhibitor might be at least 1.5, preferably between 2.5 and 3.5. Taking in account the above information and considering 200mg of the proteinase inhibitor per 1g of composition, this means that the composition would require at least 300mg but preferably between 500 and 700mg of monoglycerides.

The mixture of mono and diglycerides of medium chain (C_8-C_{10}), marketed as Akoline, used to prepare the presently claimed pharmaceutical composition contains approximately 50-62% of monoglycerides therefore different from Bailey's recommendation. This difference becomes more pronounced for the claimed compositions comprising less than 40% of the mixture of mono and diglycerides of medium chain (C_8-C_{10}) therefore out of the range taught by the Bailey reference. For instance, each 1g of the presently claimed composition of the example 5 contains 200mg of ritonavir (a proteinase inhibitor) and 234.875 mg of the mixture of mono and diglyceride of medium chain which contains about 117.43 to 145.62mg of **mono**glycerides that is much less than the minimum amount of monoglycerides taught by the document. Even the presently claimed composition of the example 1 containing 509.80mg of the mixture of mono and diglyceride of

medium chain length which contains about 254.9 to 316.1mg of monoglycerides is outside of the teachings of the Bailey reference, depending on the monoglyceride content of the Akoline batch.

So, one ordinary skilled in the art would not expect that trying to modify Lipari by the teachings of Bailey to obtain the present application composition would be successful in view of Bailey's teachings, since some embodiments of the claimed invention are contrary to Bailey's teachings.

In addition, experimental data provided in the Declaration enclosed herein clearly show that the process and compositions taught by Bailey are not suitable for producing a clear and soluble composition for ritonavir. In particular, the attached Declaration of Dr. Pacheco shows that the presently claimed process unexpectedly provides completely dissolved solutions of both polymorphs I and II of ritonavir despite employing lower concentration of mono/diglyceride mixture compared with Bailey's teachings.

Also, Lipari adds nothing to the solution of the problem of providing a stable, clear, highly concentrated composition of ritonavir.

Applicants submit that the present claims now clearly recite process steps that establish the difference between the present invention and the prior art, *i.e.* that the composition of ritonavir obtained is one having a high concentration and that is stable and clear and completely dissolved.

2 (b). Lipari in view of Bailey and CU Boulder Organic Chemistry Undergraduate Courses, Lab Techniques.

The Examiner has maintained the rejections of the process claims as allegedly unpatentable over Lipari in view of Bailey and further in view of CUBoulder Organic Chemistry Undergraduate Courses, Lab Techniques. (Office Action, page 12) The Examiner states that vacuum distillation is an elementary technique as well it is taught in high school and college. The Applicants respectfully traverse the rejection.

As pointed out in Applicants' September 14, 2007 response, process claims must be read as a whole being analyzed by all their steps and conditions. The Examiner should consider that the presently claimed process, as a whole, including steps of **complete dissolution** of ritonavir in ethanol, filtration and posterior vacuum rotary evaporation at low temperature to concentrate the solution provides the result of dissolved ritonavir, in a microcrystal-free form and at high concentration, within the remaining ingredients of the composition.

Once the ritonavir is dissolved and the solution is concentrated by the aforementioned steps, the triggering of ritonavir precipitation is prevented, and moreover, the polymorphic form interference is avoided. No prior art reference has described nor suggested such a result.

The claimed steps in sequence confer improvement over the prior art: *i.e.* the direct addition of the solid form of ritonavir to the oily solvent under vigorous stirring and higher temperatures, allowing the obtaining of the instant compositions, even if the more insoluble polymorph is employed. Furthermore, the present invention process allows the preparation of concentrated compositions and the administration regimen for this medicine can be advantageously simplified, reducing considerably the number of capsules to be administered every day.

Moreover, no prior art reference has taught or suggested the claimed steps for preparing ritonavir compositions, and the skilled artisan would not be motivated to dissolve ritonavir under low temperature to avoid ritonavir degradation, filter and then evaporate the solvent to concentrate the ritonavir in solution, since it is known that ritonavir has poor solubility.

> "*The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination*". MPEP 2143.01.

> "*A statement that modifications of the prior art to meet the claimed invention would have been 'well within the ordinary skill of the art at the time the claimed invention was made' because the references relied upon teach that all aspects of*

the claimed invention were individually known in the art is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references". MPEP 2143.01.

The following characteristics of the instant invention are inventive and can solve the state of the art problems:

- By the process of the instant invention there is no need to use the active pharmaceutical ingredient in a special crystalline form. [see page 19, lines 3-8 of the specification as filed];
- By this process, it is possible to obtain more concentrated compositions of ritonavir without precipitation of the active ingredient within the composition. The prior art processes, which involve the direct dissolution of the active ingredient, are not able to achieve such technical advance. [see page 19, lines 8-12 of the specification as filed];
- Only by this process, it is possible to obtain clear compositions of ritonavir according to the instant invention.

In summary, the instant invention includes objective evidence of nonobviousness due to the following aspects:

(1) It satisfies a long-felt need and failure of others since it can contribute for the adherence of patients to the treatment;
(2) It finds a solution to the prior art problem – to provide stable and concentrated compositions and to solve the problem of crystallization of the less soluble form of ritonavir;
(3) Unexpected results are presented in the application as filed since it shows increased stability and concentration of the final composition and, consequently, it improves the efficiency of the treatment using the active substance (ritonavir).

Accordingly applicants respectfully request reconsideration and withdrawal of the instant obviousness rejection.

3. Claim rejections under 35 USC 112

The Examiner has maintained the rejections to claims 26-36 under 35 USC 112 2nd paragraph for indefiniteness with respect to the methods of manufacture that do not state a specific concentration, weight, or final product form as an endpoint. The claims have been amended to limit the scope to the specific amount and weight ranges of the present invention. The Applicants believe that, with such amendments, the rejection is overcome.

4. Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully request immediate allowance of the claims, which define subject matter that meets all statutory patentability requirements.

If the Examiner has any questions or comments, please contact the undersigned by telephone to discuss the matter.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Dated: June 3, 2008

Respectfully submitted,

By /m/ Nuell

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PATENT
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IN THE U.S. PATENT AND TRADEMARK OFFICE

Applicant:	Ogari Pacheco et al	Conf.:	5587
Appl. No.:	10/517,453	Group:	1609
Filed:	December 9, 2004	Examiner:	Huang, G. G.
For:	SOLUBLE, STABLE, AND CONCENTRATED PHARMACEUTICAL COMPOSITIONS COMPRISING RITONAVIR AND PROCESS FOR PREPARING THEREOF (as amended)		

DECLARATION UNDER 37 CFR 1.132

Ogari de Castro PACHECO declares that:

[001]. I am a founding partner of CRISTÁLIA PRODUTOS QUÍMICOS FARMACÊUTICOS LTDA, the assignee of the entire rights title and interest in the above-identified patent application and the invention described therein.

[002]. I received a doctor degree in 1964 from the School of Medicine of the San Paulo University (in Portuguese, Universidade de São Paulo), from San Paulo, Brazil. In 1966, I received a postgraduate degree in surgery of the digestive tract from the Hospital of Clinics of the School of Medicine of the San Paulo University.

[003]. I am fully knowledgeable of the disclosure of the above-identified patent application and the field of art of the present invention. I have read and understand the December 3rd, 2007 Office Action and the references cited therein.

[004]. This declaration is made to **(I)** provide experimental data comparing the composition of the present invention with the composition from the closest prior art

reference taking in account the ingredients employed and their respective amounts from each composition, as well as the process for preparing the composition taught by the prior art reference compared with the process of the present invention which employs pre-dissolution of the active ingredient followed by filtration and vacuum rotary evaporation (hereinafter mentioned as "rotoevaporation") as the key steps for obtaining the soluble and clear ritonavir composition of the present invention; **(II)** show by way of the experimental data presented herein that the US patent 6,008,228 (hereinafter mentioned as "Bailey's reference" or just "Bailey") cannot be used to establish a *prima facie* case of obviousness since the teachings provided therein cannot be extrapolate for the compound ritonavir; and **(III)** conclude, supported by the experimental data presented herein, that there is no expectation of success for one skilled in the art to combine both references cited by the Examiner (US patent 6,232,333, and US patent 6,008,228).

(I) Experimental data comparing the present invention composition with the closest prior art reference

[005]. It was established that the closest prior art reference is the Bailey's reference, since it provides the usage of C_8-C_{10} medium chain mono/diglyceride mixture as the solvent in the composition of and HIV protease inhibitor as does the present invention composition, while the US patent 6,232,333 (hereinafter mentioned as "Lipari's reference" or just "Lipari") teaches the usage of long chain (C_{12}-C_{18}) fatty acid as solvent in the composition, being the most plentiful ingredient of the composition, which is not found in the present invention composition.

[006]. For proper comparison tests, the Bailey's composition was reproduced replacing saquinavir by ritonavir. The results are presented and discussed on the present Declaration.

[007]. The specific formulations investigated by the present tests were elected according to the proximity of ingredients and their correspondent amounts as described on each documents (Bailey's reference and the present application). The formulations investigated are described at tables 1 and 2:

Table 1 - First Comparison

Ingredient	Quantity in grams*	
	Formulation A63 from the US 6,008,228 (A63)	Formulation of Example 1 from the present application (Ex1)
Ritonavir§	40	40
Medium chain mono/diglyceride (Akoline®)	153.8	101.96
Antioxidant	0.2 (alpha-tocopherol)	0.05 (BHT)
Polyvinylpyrrolidone K30 (PVP K30)	6	-
Ethanol#	-	24
Propylene glycol	-	20
Castor oil polyethoxylated 35	-	12
Water	-	1.99
Total	200	200

* Quantities adapted for 200g of the final composition
# Final amount of ethanol within the formulation. Before evaporation it has been used 48g of ethanol for dissolving ritonavir
§ Formulations were prepared using firstly polymorph I and then polymorph II of ritonavir

PEG 400, castor oil polyethoxylated 40 and polyvynilpyrolidone K30 in a suitable vessel with stirring and heating until approximately 50°C; addition of the active ingredient (for the present test was used ritonavir in the place of saquinavir) and maintaining the stirring until total dissolution of the active ingredient within the medium if it is possible; after cooling at room temperature, it was added the dl-alpha-tocopherol to the mixture under stirring until its dissolution within the medium, if it is possible.

[0012]. The formulations of the Examples **1** and **5** (respectively **Ex1** and **Ex5**) from the present application were prepared by two different ways, in order to demonstrate the relevance of the procedure steps sequence to the final result relative to the composition appearance as described at the present application:

[0013]. **(i)** By the process described in the present application wherein, in general, ritonavir is totally dissolved in plenty amount of ethanol at 30-45°C, followed by the filtration of the resulting solution (to remove the microcrystals of ritonavir from the medium), and then concentrating the solution by rotoevaporation, wherein ethanol excess is removed under reduced pressure at a temperature of about 40°C until achieving the desired ethanol content in the final composition (12% w/w).

[0014]. **(ii)** By direct dissolution of ritonavir into the mixture of the excipients with heating until 30-45°C. In this procedure there was neither filtration nor rotoevaporation in order to demonstrate the relevance of theses steps for the final composition.

[0015]. **Results and discussion:**

[0016]. **First comparison**

[0017]. **a) A63 – Polymorph I**

[0018]. After mixing the ingredients of A63 formulation according to the afore-mentioned process, it was observed the non-dissolution of ritonavir in the medium, even after constant stirring and maintenance of temperature at ~60°C, for 12 hours:

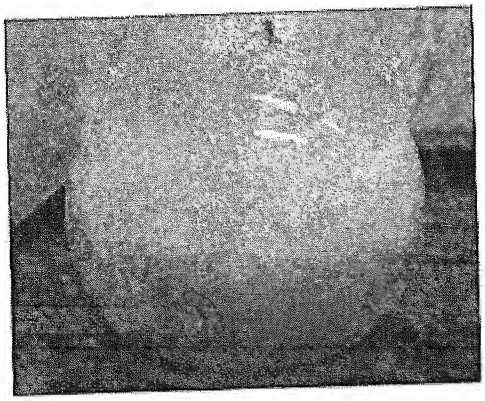


Figure 1: Formulation A63 with polymorph I of ritonavir after 12 hours of constant stirring and temperature maintained at ~60°C.

[0019]. In addition, after cooling, the suspension solidified within the flask:

Figure 2: solidification of the resulting A63 formulation

[0020]. **b) A63 – Polymorph II**

[0021]. This experiment was not performed due to the observed unfeasibility of this formulation for polymorph I of ritonavir, which is known to be more soluble than polymorph II.

[0022]. **c) Ex1 – Polymorph I – process (i)**

[0023]. The formulation from Example 1 of the present application (**Ex1**) was prepared according to the process formerly described in **(i)**.

[0024]. For illustrative comparison we provide bellow a picture showing the total dissolution of ritonavir, polymorph 1, in ethanol (**figure 3**):

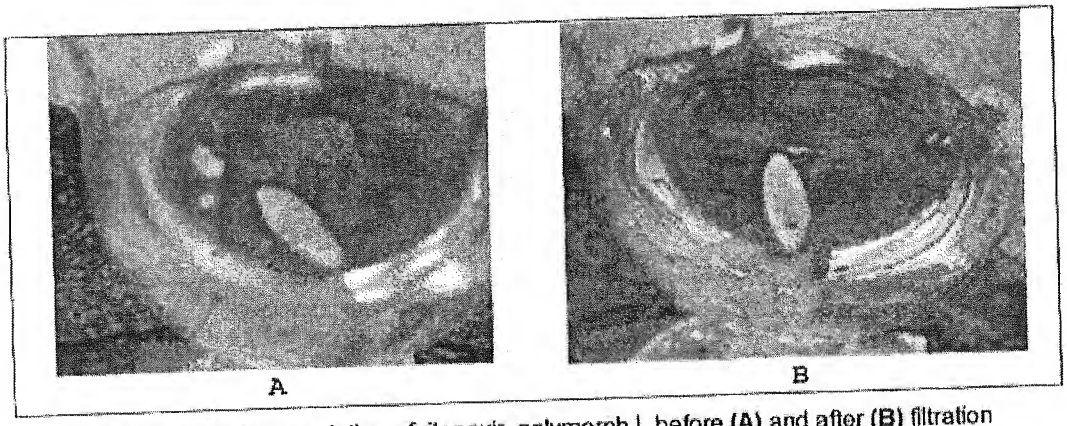


Figure 3: ethanolic solution of ritonavir, polymorph I, before **(A)** and after **(B)** filtration

[0025]. After filtration, the solution was concentrated using a rotoevaporator as illustrated below until achieving weight approximately of 64g (40g of ritonavir + 24g of ethanol):

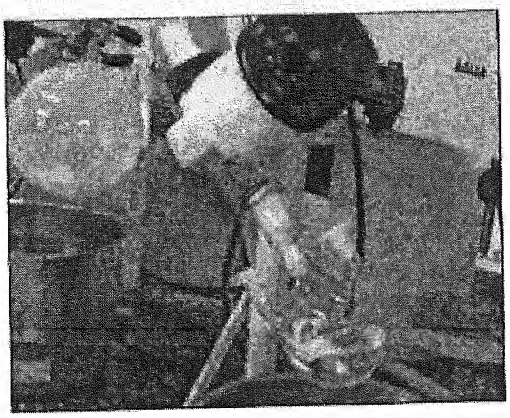


Figure 4: concentration of ritonavir ethanolic solution by rotoevaporation

[0026]. After concentration of the solution above, the others ingredients of the **Ex1** were added according to the process formerly described in **(i)**.

[0027]. The resulting formulation is illustrated bellow, wherein it is possible to note that is totally clear and soluble wherein all the components are dissolved:

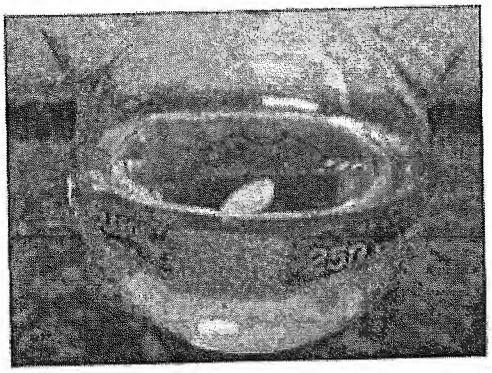


Figure 5: Final Ex1 Formulation, using polymorph I of ritonavir

[0028]. **d) Ex1 - Polymorph II - process (i)**

[0029]. The same procedure described in **(c)** was used for the **Ex1** formulation now using the polymorph II of ritonavir.

[0030]. As observed by the pictures bellow (**figure 6**), even using the more insoluble polymorph, the composition of the present application was able to adequately dissolve ritonavir, providing a final clear and soluble composition:

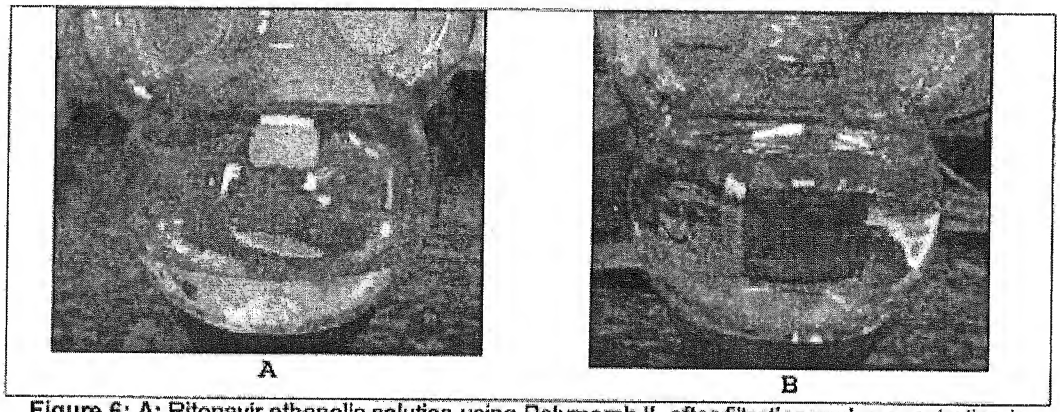


Figure 6: A: Ritonavir ethanolic solution using Polymorph II, after filtration and concentration by rotoevaporation; B: Final Ex1 composition of Polymorph II of ritonavir.

[0031]. **e) Ex1 - Polymorph I - process (ii)**

[0032]. The formulation **Ex1** of the present application was also prepared by direct-addition of the ingredients according to the process formerly described in **(ii)**. As mentioned before, we performed a simple method for preparing the **Ex1**, disregarding the present application described pre-dissolution of ritonavir in ethanol and subsequent filtration and rotoevaporation steps. This was made in order to demonstrate the relevance of such steps in the whole process of the present application for suitable results to the final composition.

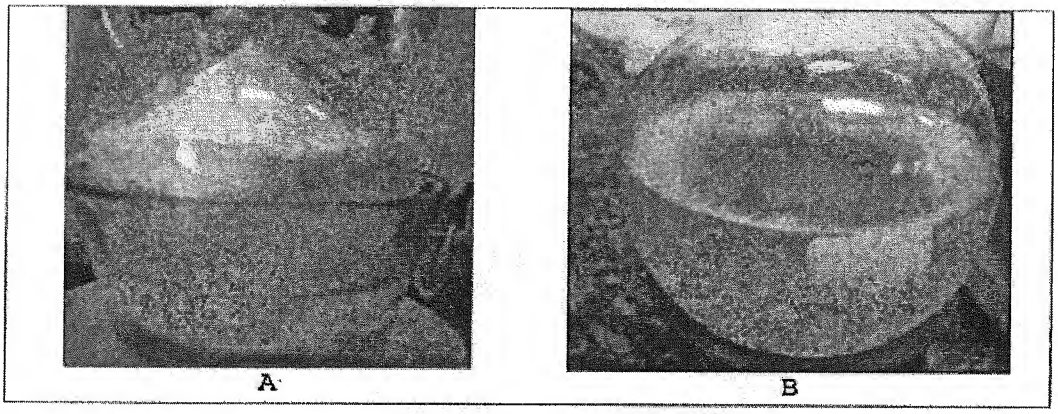


Figure 7: A: Direct-addition of the ingredients of the formulation **Ex1**; **B:** Observe the incomplete dissolution of polymorph I of ritonavir within the medium, even after constant stirring for 12 hours, at ~45°C.

[0033]. **f) Ex1 – Polymorph II – process (ii)**

[0034]. The same process of item **(e)** was accomplished for **Ex1** formulation, now using the polymorph II of ritonavir. The final composition is illustrated bellow (**figure 8**):

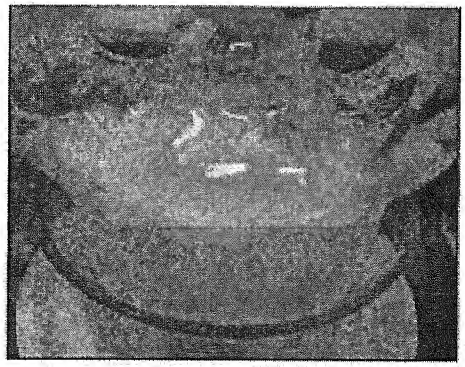


Figure 8: Observe the incomplete dissolution of polymorph II of ritonavir within the medium, even after constant stirring for 12 hours, at ~45°C.

[0035]. **Second comparison**

[0036]. **a1) A25 – Polymorph I**

[0037]. After mixing the ingredients of **A25** formulation according to the afore-mentioned process, it was observed the non-dissolution of ritonavir in the

medium, even after constant stirring and maintenance of temperature at ~60°C, for 12 hours (see **figure 9, panel A**)

[0038]. **b1) A25 - Polymorph II**

[0039]. The experiment was not performed due to the observed unfeasibility of this formulation for polymorph I of ritonavir.

[0040]. **c1) Ex5 - Polymorph I - process (i)**

[0041]. The formulation from Example 5 of the present application (**Ex5**) was prepared according to the process formerly described in **(i)**.

[0042]. The resulting formulation is illustrated in **figure 9, panel B**, wherein it is possible to note that is totally clear and soluble.

[0043]. **d1) Ex5 - Polymorph II - process (i)**

[0044]. The same procedure described in **(c1)** was used for the **Ex5** formulation now employing the polymorph II of ritonavir.

[0045]. As observed by the **figure 9, panel C**, even using the more insoluble polymorph, the composition of the present application was able to adequately dissolve ritonavir, providing a final clear and soluble composition:

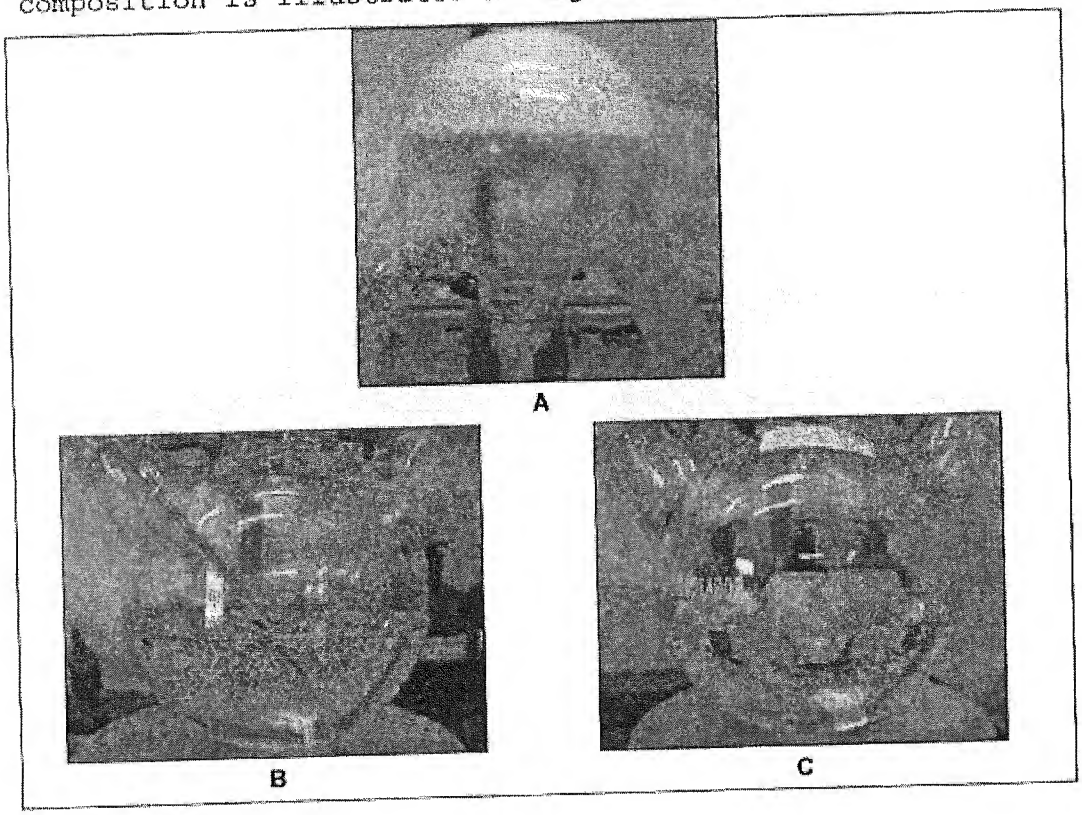
[0046]. **e1) Ex5 - Polymorph I - process (ii)**

[0047]. The formulation **Ex5** of the present application was also prepared by direct-addition of the ingredients according to the process formerly described in **(ii)**. As mentioned before, we performed a simple method for preparing the **Ex5**, disregarding the present application described pre-dissolution of ritonavir in ethanol and the subsequent filtration and rotoevaporation steps. This was

made in order to demonstrate the relevance of such steps in the whole process of the present application for suitable results to the final composition. The final composition obtained by this process, using polymorph I of ritonavir is illustrated at **figure 9, panel D.**

[0048]. **f1) Ex5 - Polymorph II - process (ii)**

[0049]. The same process of item **(e1)** was accomplished for Polymorph II **Ex5** formulation. The final composition is illustrated at **figure 9, panel E.**



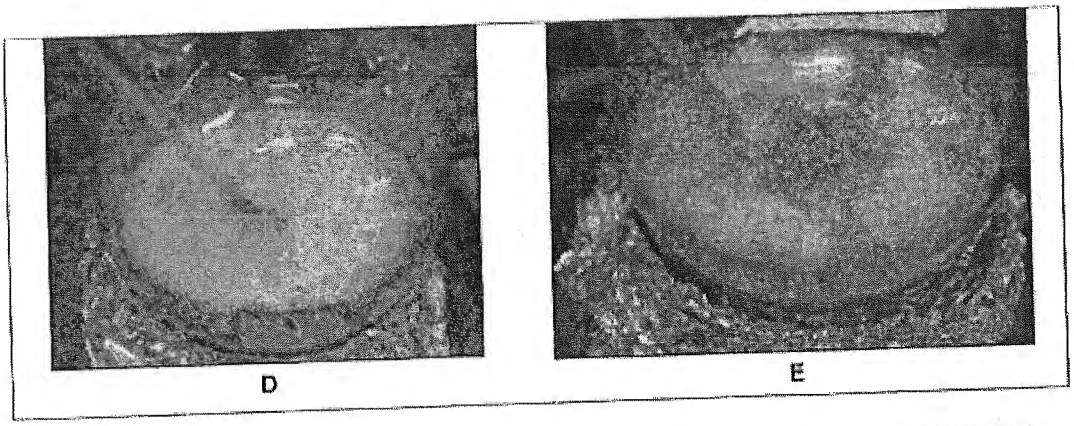


Figure 9: A: Solidified formulation A25 with polymorph I of ritonavir after 12 hours of constant stirring and temperature maintained at ~60°C; **B:** Formulation **Ex5** prepared by the process **(i)** using polymorph I of ritonavir; **C:** Formulation **Ex5** prepared by the process **(i)** using polymorph II of ritonavir; **D:** Formulation **Ex5** prepared by the process **(ii)** using polymorph I of ritonavir; **E:** Formulation **Ex5** prepared by the process using polymorph II of ritonavir.

[0050]. (II) The US patent 6,008,228 cannot be used to establish a *prima facie* case of obviousness

[0051]. The above-mentioned comparison tests clearly demonstrate that the Bailey's reference does not teaches neither ritonavir compositions nor the process for obtaining such compositions.

[0052]. The attempt to extrapolate the Bailey's compositions to be employed for ritonavir instead of saquinavir showed that it is not possible, once the resulting compositions did not present suitable appearance and dissolution of the active ingredient.

[0053]. The tests evidence that one having skill in the art cannot be able to produce clear and soluble compositions of ritonavir using the Bailey's teachings.

[0054]. Therefore, the Bailey's reference cannot be used to establish a *prima facie* case of obviousness in the present case.

[0055]. **(III) There is no expectation of success for one skilled in the art to combine both references cited by the Examiner (US patent 6,232,333 in view of and US patent 6,008,228)**

[0056]. Based on the experimental data provided herein, it is clear that one skilled in the art had no expectation of success for the simple usage of a mixture of medium chain mono/diglyceride to dissolve ritonavir.

[0057]. The proper compositions according to the present application cannot be made simply following the previous description of excipients individually. Actually it depends on several other factors that must be considered, such as the amount of the mono/diglyceride mixture employed; the specific combination with the elected excipients and with their relative proportions; the order of addition of the elements in the preparation of the composition; the whole process for the preparation of the compositions, specifically including the steps of pre-dissolution of ritonavir, filtration and rotoevaporation for concentrating it; among others. The Bailey's reference did not taught neither suggested such factors, and so, if the skilled artisan followed Bailey's teachings, he would achieve only the improper ritonavir compositions as showed in the **figures 1, 2, and 9A.**

[0058]. Lipari's reference does not taught the process steps or the combination of the excipients of the present application. The plentiful ingredient of Lipari's

compositions is long chain fatty acids, specifically oleic acid, and it is not employed in the present application composition.

[0059]. Considering the arguments above, we believe that the combination of Bailey's reference and Lipari's reference is hindsight, and one with skill in the art cannot be motivated to combine both references neither to replace a long chain fatty acid by a medium chain mono/diglyceride mixture with reasonable expectation of success.

Statement

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed by me in Itapira-San Paulo, Brazil, this 29th day of May, 2008

Ogari de Castro PACHECO